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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,783	08/21/2003	Nancy C. Lan	1483.0370003	6918

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/644,783	LAN, NANCY C.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2006* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-52* is/are pending in the application.

4a) Of the above claim(s) *22-33 and 46-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-21,34-45 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *05/15/06* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's Response filed May 15, 2006 in response to O.A. mailed December 13, 2005.

2. Claims 10-52 are currently pending in the application, but claims 22-33 and 46-49 were withdrawn from consideration as being drawn to the non-elected invention. Claims 10-21, 34-45 and 50-52 are currently pending for prosecution on the merits of the instant application.

Response to Arguments

3. Applicant's arguments with respect to claims 10-21, 34-45 and 50-52 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10-21, 34-45 and 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating or ameliorating the specific chronic pain such as neuropathic pain, does not reasonably provide enablement for treating or preventing "chronic pain". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

With respect to the scope of enablement for "prevention" of chronic disease,

The claims read on use of a pharmaceutical composition comprising a sodium channel - blocker such as 4-(4'-fluorophenoxy)benzaldehyde semicarbazone in combination with gabapentin for the treatment, prevention or amelioration of chronic pain.

Websters II Dictionary defines the term "prevent" as "anticipate or counter in advance, to keep from happening". The interpretation of the instant claims allows for the complete cure and eradication or total elimination of chronic pain by the administration of said agents.

It is generally known in the art that some treatments (e.g., opioids, steroids, NSAIDs, anticonvulsants, local anesthetic, tricyclic antidepressants and etc...) may shorten the duration or lessen the severity of symptoms of some chronic pains. However, no treatment has been shown to prevent chronic pain. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits of the instant application. For example, there is no known cure for trigeminal neuralgia and postherpetic neuralgia. Nor there is one test

to properly diagnose trigeminal neuralgia or postherpetic neuralgia yet. The true fact of the state of the art is illustrated succinctly in the "Trigeminal Neuralgia", www.enwikipedia.org, 2006; "About Post-Herpetic Neuralgia", www.aftershingles.com, 2000"; "Herpes Zoster and Postherpetic Neuralgia", Mousey et al., American Family Physician, 2005, Vol 72. No.6, pp. 1075-1080; "Postthepetic Neuralgia", Zagaria M.A., US. Pharmacist, 2002, Vol. 27, No. 10; and Treatment of Trigeminal Neuralgia at Mayo Clinic", www.mayoclinic.org. 2006. Thus, it is beyond the skill of pharmacologists today to get an agent to be cure or completely eliminate the condition encompassed by the claimed invention.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the preventive utility of the instant drug combination. Therefore, it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" or completely cure or eradication effect.

The claims are very broad. The scope of the instant claims encompasses prevention (complete thwarting or warding off illness or total elimination or eradication of disease) of any types of chronic pain that may have different underlying mechanism, for example (i) pain due to inflammatory pain or postoperative pain, (ii) neuropathic pain (e.g., trigeminal neuralgia, diabetic neuropathy, herpetic neuralgia, etc...), (iii) cancer pain and (iv) idiopathic pain.

The specification provides study showing the coadministration of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (Co 102862) and gabapentin in the Chung model of

neuropathic rats. However, there is no demonstrated correlation that the tests and results apply to the preventive utility embraced by the instant claims.

Since the efficacy of the instantly claimed drug combination in preventing the chronic pain mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to scope of enablement for the "treatment of chronic pain",

The claims read on use of a pharmaceutical composition comprising a sodium channel - blocker such as 4-(4'-fluorophenoxy)benzaldehyde semicarbazone in combination with gabapentin for the treatment of chronic pain.

By definition, chronic pain refers to pain that persists and includes various types of pains that may have different underlying etiology and pathophysiology including inflammatory pain, postoperative pain, osteoarthritis pain, trigeminal neuralgia, acute herpetic neuralgia, acute postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout pain, phantom limb pain, burn pain and etc... For example, chronic pain due to inflammatory pain or postoperative pain or cancer pain (nociceptive pain) differs from neuropathic pain that caused by abnormalities in the nerves, spinal cord or brain. Also, treatment of neuropathic pain differs from the treatment of nociceptive pain.

Because of their different etiology, pathophysiology, diagnosis and treatment modality, it is known that no examples exist for efficacy of a single product against all types of chronic pain. The existence of such a "silver bullet" is contrary to our present understanding of pharmacology. Thus, it is beyond the skill of pharmacologists today to get an agent to be effective against all types of chronic pain.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the treatment of all of chronic pain by the administration of the instant drug combination. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

As discussed above, the instant claims embrace the therapeutic treatment of all types of chronic pain that may have different underlying mechanism, for example (i) pain due to inflammatory pain or postoperative pain, (ii) neuropathic pain (e.g., trigeminal neuralgia, diabetic neuropathy, herpetic neuralgia, etc...), (iii) cancer pain and (iv) idiopathic pain.

The specification provides study showing the coadministration of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (Co 102862) and gabapentin in the Chung model of neuropathic rats. As discussed above, the treatment of neuropathic pain differs from inflammatory pain, postoperative pain, cancer pain, phantom limb pain and idiopathic pain. Thus, one having ordinary skilled in the art would have not known how to treat inflammatory

pain, postoperative pain, cancer pain, phantom limb pain and idiopathic pain, without undue amount of experimentation.

In view of limited numbers of working examples, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the breadth of the claim and the relative skills of the artisan and the unpredictability of the pharmaceutical art where different treatment modalities are existed among different types of chronic pain would take "undue painstaking experimentation" to practice the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "substantially" in claim 17 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining what is meant by "substantially simultaneously", and one of ordinary skill in the art would not be reasonably apprised of the scope of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 10-21, 34-45 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (WO 9847869) in view of Rosenberg et al. (The Clinical Journal of Pain, 13:251-255, 1997), and further in view of Bueno (US 6242488) and Caruso et al. (US 6187338).

The claims read on use of a pharmaceutical composition comprising a sodium channel - blocker such as 4-(4'-fluorophenoxy)benzaldehyde semicarbazone in combination with gabapentin for the treatment, prevention or amelioration of chronic pain, more specifically "trigeminal neuralgia", "diabetic neuropathy" and "cancer pain". Further limitation includes the administration of said drug(s) in "simultaneously" or "separately" (claim 17 or 18 respectively); "said first agent and said second agent are administered as part of a single pharmaceutical preparation (claim 19); various delivery dosage forms including oral (claims 21 and 40), parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal or buccal forms (claims 50 and 51).

Wang teaches the use of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone for ameliorating chronic pain, neuropathic pain such as trigeminal neurologia or diabetic neuropathy (abstract; page 1 line 15 thru page 2, line 22; page 3, lines 27-28; page 4, line 4; page 25, lines 13-14; claims 1, 5, 7-8), wherein said compound is administered in the dosage range of 0.0025 to 50mg/kg orally or about 0.25 to about 10mg/kg intravenously (page 28, lines 3-23); and wherein said compound is prepared in various pharmaceutical dosage forms including oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal and buccal forms (page 29, line 13-20). Wang also teaches the use of sodium channel blocker (e.g., carbamzepine and lamotrigine) for treating neuropathic pain due to trigeminal neurologia and diabetic neuropathy (page 2, lines 5-22).

Rosenberg teaches the use of GABA analogs such as gabapentin for the treatment of chronic pain such as neuropathic pain (e.g., postherpetic neuralgia, diabetic neuropathy), wherein median dose of 600-2400mg, orally, is administered for the treatment of neuropathic pain (abstract; Table 1; results).

Bueno is being supplied as a supplemental reference to demonstrate the routine knowledge in preparing gabapentin in various dosage forms including oral, parenteral and intravenous administration (column 3, line 66 thru column 4, line 5).

Caruso is being supplied as a supplemental reference to demonstrate the routine knowledge in art in determining the delivery of various neuropathic pain-alleviating active ingredients including gabapentin in combination by separate administration or coadministration in single dosage forms (column 2, line 36; column 5, lines 8-14).

The teaching of Wang differs from the claimed invention (i) mainly in the combination use of sodium channel blocker such as 4-(4'-fluorophenoxy) benzaldehyde semicarbazone and gabapentin in treating chronic pain, namely "trigeminal pain", "diabetic neuropathy" and "cancer pain"; (ii) the specific dosage amounts of each active ingredients, and (iii) the delivery of said combination in various dosage forms including oral, parenteral, intravenous, inmuscular, intraperitoneal, transderal or bucal forms and the specific order of delivery of said combination.

With respect to the combination of sodium channel blocker such as 4-(4'-fluorophenoxy) benzaldehyde semicarbazone and gabapentin for the treatment of chronic pain,

To incorporate such teaching into the teaching of Wang, would have been obvious in view of Rosenberg who teaches the use of gabapentin for treating chronic pain such as neuropathic pain (e.g., neuralgia, diabetic neuropathy).

The above references in combination make clear that the sodium channel blocker (i.e., 4-(4'-fluorophenoxy)benzaldehyde semicarbazone) and gabapentin have been individually used for the treatment of chronic pain such as neuropathic pain. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

One having ordinary skill in the art would have been motivated to modify the teaching of Rosenberg such that the pharmacological activity of gabapentin would be enhanced by the addition of sodium channel blocker such as 4-(4'-fluorophenoxy)benzaldehyde semicarbazone

while toxicity associated with high dose of gabapentin would be minimized by the combination of said sodium channel blocker. One having ordinary skill in the art would have expected that the claimed combination would be useful in treating chronic pain due to trigeminal neuralgia and diabetic neuropathy in view of combination of Wang and Rosenberg.

With respect to the optimization of dosage amounts of each ingredients, dosage forms and concurrent administration regimen,

Those of ordinary skill in the art would have been readily determined the optimum dosage amounts or drug delivery forms (e.g., oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal or buccal) or the order of administration (e.g., simultaneously, separately) by good medical practice and the clinical condition of the individual patient. One having ordinary skill in the art would have been motivated to determine optimum amounts of known active ingredients to maximize the efficacy of drugs while minimizing the adverse effects of the drugs. Determination of the appropriate dosage forms or frequency regimen for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of known therapeutic dosage amounts of each active ingredients and available dosage forms of said drugs in the art.

One having ordinary skilled in the art would have been motivated to make such modification to extend the usage of the claimed composition to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated drug. As discussed in preceding comments, such determination of optimal ranges of effective

amounts of each component, dosage forms and concurrent administration regimen is well considered within the skill of the artisan, absent evidence to the contrary.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system,

see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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